The function of YAP in human embryonic stem cells

Grant Award Details

The function of YAP in human embryonic stem cells

Grant Type: Basic Biology II

Grant Number: RB2-01547

Project Objective: major goal of this study is to examine the regulation of the Hippo pathway, to investigate the role of Hippo-YAP regulation in stem cells, and to identify and characterize small compounds that can either activate or inhibit the Hippo pathway.

Investigator:

Name:	Kun-Liang Guan
Institution:	University of California, San Diego
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: Embryonic Stem Cell, iPS Cell

Award Value: $1,245,693

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title:	The function of YAP in human embryonic stem cells
Public Abstract:	Embryonic stem cells have the potential to generate all tissue types that could be used for regenerative medicine, such as replacement of damaged neurons, replenish of insulin secreting beta cells, or generation of blood cells. The discovery of in vitro reprogramming of somatic cells (normal cells in our body) into induced pluripotent stem cells (iPS, which has the potential to differentiate into many different cell types) offers an exciting reality that patient specific pluripotent stem cells could be obtained. Cells derived from patient specific iPS cells would less likely to cause immune rejection when transplanted back into the patient. The rapid progresses in stem cell research make regenerative medicine from scientific fiction close to medical reality. However, many key issues, such as the efficiency of iPS induction and efficiency of stem cell differentiation in vitro (outside of our body), remain to be resolved before stem cell therapy becomes a routine medical practice. YAP is a transcription co-activator, which can help certain transcription factors to stimulate gene expression. Previous studies have shown that elevated YAP activity makes organ bigger. For example, YAP overexpression in mouse livers increases liver size by 4-5 fold. High YAP activity has also been observed in some human caners. We have found that YAP has an important role in mouse embryonic stem cells. Decreased YAP activity forces stem cell to differentiate while high YAP activity maintains stem cell properties even under differentiation conditions. We also found that in mouse embryonic stem cells YAP stimulates expression of many genes known to be important for stem cell pluripotency. In this project, we will study the function of YAP in human embryonic stem cells. We hope to understand how YAP promotes the stem cell properties. In addition, we would like to know how YAP itself is regulated in the human embryonic stem cells, by specifically determining YAP protein levels, localization in the cell, and degradation. Finally, we will isolate YAP activators and inhibitors. YAP activators may help us more efficiently generating iPS cells from somatic human cells. Conversely, YAP inhibitors may facilitate in vitro differentiation of human embryonic stem cells, therefore reduce the risk of teratoma formation caused by residual undifferentiated ESC in stem cell therapy. Completion of this project will help us to understand the basic biology of stem cells and may provide candidates for future drug development.
Statement of Benefit to California:	Stem cell therapy has the potential to revolutionize the treatment of many common diseases that afflict residents of the State of California. Alzheimer's disease, diabetes, heart failure, anemia and arthritis are just a few of the illnesses that could potentially be treated. The benefits of the proposed research to the State of California and to its residents will be multiple. It will accelerate the pace of stem cell research, by discovering the novel function of YAP in human embryonic stem cells. The function of YAP in embryonic stem cells has not been reported while our preliminary study strongly indicates a success of this project. Our study will provide scientific knowledge of ESC stemness maintenance and research tools to more efficiently reprogramming iPS from normal somatic human cells. This would facilitate generation of patient-derived iPS cells. Moreover, as we hypothesized, inhibition of YAP activity will deplete human embryonic stem cells in in vitro differentiation; therefore decrease the risk of tumor formation in receipt patients. This project will generate knowledge beneficial to stem cell therapy and provide drug candidates for regenerative medicine in the state of California.